THE BIOLOGICAL INTERRELATIONSHIPS OF CERTAIN AMINO ACIDS

BY
THOMAS ROSS WOOD
B.S., University of Denver, 1937

AN ABSTRACT OF A THESIS
SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
CHEMISTRY IN THE GRADUATE SCHOOL OF
THE UNIVERSITY OF ILLINOIS, 1940

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The author wishes to express his sincere appreciation for the guidance and encouragement of Professor William C. Rose, who suggested these problems.

PART I

THE IN VIVO SYNTHESIS OF CYSTINE

INTRODUCTION

The literature contains a large body of indirect evidence which indicates that cystine can be synthesized in the animal body. White and Lewis (1932) have shown that methionine is as effective as cystine in promoting the detoxication of bromobenzene. Methionine, as well as homocysteine, gives rise to extra urinary cystine when ingested by a cystinuric (Brand, Cahill, and Harris, 1935). Furthermore, Womack, Kemmerer, and Rose (1937), employing a mixture of purified amino acids, have shown that rats are able to grow at optimum rates when fed a cystine-free diet containing methionine.

The goal sought in the present work has been a direct proof of the *in vivo* synthesis of cystine. This has been attempted by conducting a study of the tissue deposition of cystine by growing rats on a diet low in cystine, but adequate with respect to methionine. This quantity was compared to the deposition of cystine by litter mate controls receiving both amino acids.

EXPERIMENTAL

Young albino rats were employed as the experimental animals. The diets, which varied in their methionine and cystine contents, were adequate in all other respects. The nitrogen was supplied in the form of highly purified amino acids. Each of four litters was divided into three groups. The first group served as controls. These were killed and analyzed for cystine at the beginning of the feeding period. The second group was allowed to grow on a ration containing adequate quantities of cystine and methionine, while the third received no cystine (with the exception of minute but known traces present in the vitamin supplement), and sufficient methionine to render the intake of sulfur identical with that of the second group. After a period of 36 to 48 days, the animals were killed and analyzed *in toto* for cystine. By comparing the total cystine present in the tissues of the animals in the third group with the average quantity in the control animals, and correcting for the maximum

amount present in the vitamin pills, an average daily synthesis of 4 to 6 mg. was demonstrated.

SUMMARY

Feeding experiments with mixtures of highly purified amino acids have furnished direct proof of the *in vivo* synthesis of cystine.

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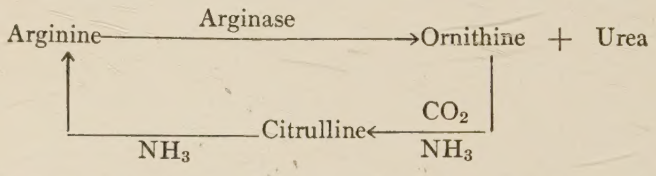
PART II

THE METABOLIC INTERRELATIONSHIP OF ARGININE, ORNITHINE, AND CITRULLINE

INTRODUCTION

The synthesis of arginine in the rat has been established by Scull and Rose (1930), employing a principle similar to that outlined in Part I of this abstract. Their animals deposited in the tissues 2 to 3 times the amount of arginine ingested during the growth period. Although the rat is able to synthesize arginine, the latter has been shown in this laboratory to be essential for *normal* growth in this species (Gunther and Rose, 1936). Animals deprived of the amino acid gained at a rate approximately 70 to 80 per cent of that of controls. Doubtless this is due to the fact that the quantity of arginine required for normal growth is slightly greater than that which can be synthesized by the organism.

In view of evidence obtained from tissue slice studies, Krebs and Henseleit (1932) have postulated the "ornithine cycle" mechanism of urea formation:



Several other investigators have presented data consistent with this concept.

If this mechanism actually takes part in the formation of urea, it is to be expected that ornithine and citrulline are interchangeable with arginine in metabolism. In the present study, the growth-stimulating properties of these three amino acids have been compared.

EXPERIMENTAL

By the use of mixtures of highly purified amino acids, a ration extremely low in arginine has been devised. The growth rates of rats supplied with such a diet have been compared to those of animals whose food contained either arginine, ornithine, or citrulline. In our experience, animals furnished the arginine-low diet have grown at a rate approximately 85 to 88 per cent of that of litter mates receiving this amino acid. As pointed out above, investigations by Gunther and Rose have appeared to indicate a slightly more pronounced effect following arginine administration. Rats deprived of this amino acid gained at a rate approximately 70 to 80 per cent of that of controls receiving the compound. In an attempt to discover the cause of this apparent discrepancy, tests have been conducted in which two different vitamin supplements were employed, and others in which the commercial dextrin ordinarily used was replaced by a highly purified preparation. None of these trials has furnished results different from those obtained previously. It is hoped that further studies which are now in progress will yield a satisfactory answer to this problem.

A study of the growth stimulating properties of ornithine and citrulline has demonstrated that the former is incapable of increasing the rate of gain of animals on an arginine-free diet, whereas citrulline is as effective in this respect as arginine itself.

SUMMARY

The relative value of the three structurally related amino acids arginine, ornithine, and citrulline has been determined by feeding them as supplements to a ration containing all of the dietary essentials except arginine. Under such conditions ornithine does not promote the growth of rats. Arginine and citrulline, on the other hand, are effective in promoting normal increases in weight.

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VITA

The author was born May 7, 1916, in Portland, Colorado. He attended the public schools of Denver, Colorado, and graduated from South Denver High School in 1933. During the period 1934-1937 he held a research assistantship at the University of Denver, and in 1937 received the degree of Bachelor of Science from that institution. In the fall of 1937 he entered the Graduate School of the University of Illinois, and from that time until 1940 has held a Special Research Assistantship in Biochemistry.

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